

Outcomes of Pre-Existing Diabetes Mellitus in Breast, Colorectal, and Prostate Cancer

Outcomes of Diabetes in Cancer

Robert I. Griffiths, ScD, MSc^{1,2}; José M. Valderas, MD, PhD, MPH³; Emily C. McFadden, PhD, MSc¹; Clare R. Bankhead, DPhil, MSc¹; Bernadette A. Lavery, BMBCh, MRCP, FRCR, MBA^{4,5}; Nada F. Khan, MBBS, DPhil, MSc⁶; Richard J. Stevens, PhD, MSc^{1,9}; and Nancy L. Keating, MD, MPH^{7,8,9}.

1. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX2 6GG.
2. Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore 21205 USA.
3. Health Services & Policy Research Group and Exeter Collaboration for Primary Care (APEX), University of Exeter, Exeter EX4 4SB.
4. Oxford University Hospitals NHS Trust, Oxford OX3 9DU.
5. Thames Valley Strategic Clinical Network, NHS England.
6. Royal Liverpool University Hospital, Liverpool L7 8XP.
7. Department of Health Care Policy, Harvard Medical School, Boston 02115 USA.
8. Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston 02115 USA.
9. Co-Senior Authors.

Corresponding Author:

Robert I. Griffiths, ScD, MSc

Nuffield Department of Primary Care Health Sciences, University of Oxford

Radcliffe Primary Care Building, Radcliffe Observatory Quarter

Woodstock Road, Oxford OX2 6GG

Tel: +44(0)1865 289300

robert.griffiths@conted.ox.ac.uk

Abstract

Purpose: Pre-existing diabetes is associated with increased morbidity and mortality in cancer, but there is less information on how cancer impacts diabetes outcomes. We examined the impact of incident cancer on long-term outcomes of diabetes. **Methods:** Using the United Kingdom Clinical Practice Research Datalink, we identified three cohorts of diabetes patients subsequently diagnosed with breast, colorectal, or prostate cancer, who were matched to diabetic non-cancer controls on age, sex, and general practice identification number. Patients were required to have survived at least one year after cancer diagnosis (cases) or a matched index date (controls), and were followed up to 10 years for incident microvascular (chronic kidney disease, nephropathy, neuropathy, retinopathy) and macrovascular (acute myocardial infarction, cerebrovascular accident, lower limb amputation, and peripheral arterial disease) complications, and mortality. Multivariate competing risks regression analyses were used to compare outcomes between cancer patients and controls. **Results:** Overall, there were 3,382 cancer patients and 11,135 controls with 59,431 person-years of follow-up. In adjusted analyses, there were no statistically significant ($p \leq 0.05$) differences in diabetes complication rates between cancer patients and their controls in any of the three cancer cohorts. Combined, cancer patients were less likely (adjusted Hazard Ratio [HR] 0.88; 95%CI=0.79-0.98) to develop retinopathy. Cancer patients were more likely to die of any cause (including cancer), but prostate cancer patients were less likely to die of causes associated with diabetes (HR 0.61: 95%CI=0.43-0.88). **Conclusions and Implications:** There is no evidence that incident cancer had an adverse impact on the long-term outcomes of pre-existing diabetes. These findings are important for cancer survivors with pre-existing diabetes because they suggest that advances in cancer therapy and supportive care, which have substantially improved the relative survival of many of the most common types of cancer, are not undermined by excess diabetes morbidity and mortality.

Abstract Word Count: 249 (excluding additional statement on implications for cancer survivors as requested by reviewer)

Keywords (MeSH terms): Diabetes Mellitus; Breast Neoplasms; Colorectal Neoplasms; Prostatic Neoplasms; Outcome Assessment (Health Care); Diabetes Complications; Mortality; Epidemiology.

Introduction

Evidence from epidemiologic studies, as summarized in a number of recent reviews, (1-10) indicates pre-existing diabetes is associated with worse short and long-term outcomes of cancer, both overall (9,10), and in specific types of cancer including breast, (3,4,10) colorectal, (2,3,4-7,10) and prostate. (8) There are several reasons why the converse also may be true—that incident cancer adversely impacts the outcomes of pre-existing diabetes. Potential mechanisms include adverse effects of cancer treatments on glycemic control, (11,12) the impact of cancer on patient self-management of diabetes, (13) and changes in the quality of diabetes primary care services during cancer treatment and follow-up. (14-19) However, there is considerably less information on how cancer impacts the long-term outcomes of pre-existing diabetes. (12, 20)

This gap in our understanding of how cancer impacts pre-existing diabetes is important from several perspectives. For instance, as early detection and advances in cancer therapy and supportive care have substantially improved the relative survival of many of the most common types of cancer, (21) overall morbidity and mortality in cancer depend increasingly on the quality and outcomes of primary care for other underlying conditions (22). In response, cancer organizations, such as Cancer Research UK and Macmillan Cancer Support in the United Kingdom (UK), have expressed concern that overlooking other medical conditions during cancer treatment and follow-up could result in excess morbidity and mortality, thereby undermining gains associated with early detection and treatment of cancer. (23,24)

The objective of this study was to examine the effect of cancer on the long-term outcomes of pre-existing diabetes.

Methods

Study Design and Data Source

We conducted an historical cohort study using the UK Clinical Practice Research Datalink (CPRD) linked to Office for National Statistics (ONS) mortality data. The CPRD contains anonymised information from general practitioner (GP) practices on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours, and referrals to secondary care for over 11.3 million patients from 674 practices in the UK. (25) There are 4.4 million active (alive, currently registered) patients in the database, which is approximately 6.9% of the UK population. These patients are broadly representative of the UK general population in terms of age, sex, and ethnicity. (25) This database (including its predecessor, the General Practice Research Datalink) has been used extensively for health services and epidemiologic research in cancer and diabetes. (26-30)

Patient Selection

Using CPRD, we identified three cohorts of cancer patients with pre-existing diabetes, each matched to diabetic non-cancer controls. Cancer patients (cases) were included if they met all of the following criteria: (A) diagnosed with breast, colorectal, or prostate cancer on or after January 1st, 2000; (B) diagnosed with type I or type II diabetes at least two years before their date of cancer diagnosis (index date); (C) had no other cancer diagnosis, except non-melanoma skin cancer, before their index date; (D) were age ≥ 50 years at their index date; (E) had at least two years of eligible CPRD data before their index date; (F) had an index date before the end of the eligible CPRD data; and (G) survived and were otherwise eligible for follow-up one year after cancer diagnosis. Patients were required to have been age ≥ 50 years at their index date because diabetes in older adults is linked to higher mortality, (31) and because older adults with diabetes are at substantial risk for both acute and chronic microvascular and cardiovascular complications (32). Men with breast cancer were excluded. Read codes from the Department of Health, Data and Business (QOF) Rules, Cancer and Diabetes Indicator Sets, version 25.0, (33) were used to identify diabetes and cancer in CPRD.

Control selection: matching

Each cancer patient (case) was matched to up to four non-cancer patients (controls) with pre-existing diabetes on GP practice number, sex (colorectal only), and age (± 1 year) at cancer diagnosis. Matched controls were also required to have met inclusion criteria D–G above. In addition to the three cohorts of breast, colorectal, and prostate cancer patients plus non-cancer controls, a fourth cohort was constructed by combining the three individual cohorts.

Patients were followed up to 10 years after their index date for new microvascular and macrovascular complications (as described below). They were followed from one year after their index date up to 10 years for all-cause and diabetes mortality.

Variables

Diabetes Complications

Complications of diabetes consisted of incident microvascular and macrovascular conditions (34) first identified in patients' electronic health records up to 10 years after their index date. Microvascular conditions consisted of retinopathy, neuropathy, nephropathy, chronic kidney disease (Stage 4 or 5), and the composite outcome of any of the four above. Macrovascular complications consisted of peripheral arterial disease, acute myocardial infarction or coronary syndrome, cerebrovascular accident, lower limb amputation, and the composite outcome of any of the four above. Incident complications were identified using published lists of Read codes (35) present in patients' records up to 10 years after their index date. Those patients identified with a specific complication prior to their index date were excluded from the population at risk for *that* complication during follow-up.

Mortality

Variables were constructed for all-cause and diabetes mortality, which was defined as the presence of an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code in the ONS data indicating that the underlying cause of death was due to diabetes (ICD-10-CM E10-14), hyperglycaemia (R73), hypoglycaemia (E16.1, E16.2), myocardial infarction

(I21-I22), ischaemic heart disease (I20, I24, I25), stroke/sequelae (I60-I64, I69.0-I69.4), heart failure (I50), sudden death due to cardiac arrest (I46), peripheral vascular disease (I70-I74), or kidney disease (N00-N28). (36,37)

Covariates

Baseline characteristics consisted of age at index date, sex, calendar year of index date, most recent (before the index date) smoking status, most recent drinking status, and index of multiple deprivation quintile, from least deprived (=1) to most deprived (=5), body mass index (kg/m²) and Charlson Comorbidity Index. (38,39) Baseline clinical and laboratory values consisted of blood pressure (mm Hg), total cholesterol (mmol/L), and glycosylated hemoglobin (HbA1c: mmol/mol), identified with the use of the most recent value within one year before the index date. Categorical variables for laboratory values were constructed by using cutoffs that corresponded to the thresholds for meeting the laboratory-based performance indicators in the QOF Rules, Diabetes Indicator Set, version 25.0, (33): blood pressure $\leq 140/80$ mm Hg, total cholesterol ≤ 5 mmol/L, and HbA1c ≤ 59 , $59\text{--}\leq 64$, $64\text{--}\leq 75$, and >75 mmol/mol. Baseline antidiabetic agents were identified with the use of British National Formulary codes in the CPRD therapy file (40) within one year before the index date.

Statistical Methods

Since there was a reasonable chance overall mortality would be higher in cancer patients than controls, we used competing risks regression according to the approach proposed by Fine and Gray (41) to estimate the cumulative incidence function and unadjusted and adjusted hazard ratios (HR) for each microvascular and macrovascular complication, comparing cancer patients to non-cancer controls. Patients were censored at 10 years after their index date or at the end of their eligibility for follow-up in the data, whichever came first. The competing risk was death prior to the date of censoring. Adjusted analyses included baseline demographic and clinical covariates as described above. Patients with a specific diabetes complication prior to their index date were excluded from that particular analysis.

Competing risks regression (41) also was used to estimate unadjusted and adjusted HRs for all-cause and diabetes mortality. Only patients eligible for linkage to the ONS data were included in the mortality analyses. Also, since study inclusion criteria required patients to have survived at least one year after their index date, survival analyses included only years 2-10 of follow-up.

Results

Overall, there were 14,517 patients in the combined cohort: 3,382 (23.3%) cancer patients and 11,135 (76.7%) controls. (Table 1) There were no statistically significant differences in age, sex, and year of diagnosis between cancer patients and controls, because age and sex were used as matching criteria in constructing the cohorts, and controls received the same index date as their corresponding cases. There were small but statistically significant ($p \leq 0.05$) differences between cancer patients and controls in the distributions of smoking status, BMI, and Charlson Comorbidity Index. (Table 1) There were no differences between cancer patients and controls in mean baseline blood pressure or HbA1c. Cancer patients had statistically significantly lower mean baseline total cholesterol than controls. (Table 1) However, the absolute difference was only 0.1 mmol/L.

The total number of years of follow-up in the combined cohort was 59,431, 13,372 (22.5%) of which were for cancer patients. Overall, the median length of follow-up was 1,495 days (4.1 years), and follow-up was statistically significantly shorter in cancer patients (median 1,444 days) than in controls (median 1,511 days: log-rank test for equality of survivor functions, $p < 0.0001$).

Diabetes Complications

There were no differences between cancer patients and controls in the adjusted rate of any microvascular or macrovascular complication, (Figure) either in the combined cohort or in any of the three cancer cohorts, (total of 80 unadjusted and adjusted comparisons) except that in the combined cohort, and only in the colorectal cancer cohort, cancer patients were less likely to develop retinopathy (adjusted HRs 0.88; 95%CI=0.79-0.98 and 0.81 95%CI=0.66-0.91 respectively). The results of sensitivity analyses in which a variable specifying the type of diabetes (Type I or Type II) was added to the list of predictors in the adjusted models were virtually identical to those reported above (results not shown).

Mortality

All-cause mortality was statistically significantly higher in cancer patients than controls (Table 3). However, there was no evidence cancer adversely impacted diabetes-related mortality. Diabetes-related mortality was significantly lower among cancer patients in the combined cohort (adjusted HR 0.76; 95%CI=0.61-0.94) and in the prostate cancer cohort (adjusted HR 0.61; 95%CI=0.43-0.88). (Table 3) The results of sensitivity analyses in which a variable specifying the type of diabetes (Type I or Type II) was added to the list of predictors in the models were virtually identical to those reported above (results not shown).

Discussion

Evidence indicates pre-existing diabetes is associated with worse outcomes in several types of cancer. However, there is less information on whether incident cancer is associated with worse diabetes outcomes. This is an important gap because as the relative survival for many types of cancer continues to improve, overall survival depends increasingly on the quality and outcomes of care for other underlying conditions. Overall, this study suggests that in the UK there is no reason to suspect that the outcomes of diabetes in the presence of cancer are adversely affected by the competing needs of cancer care.

Among 80 unadjusted and adjusted comparisons of diabetes complications, we found no instance in which cancer was associated with higher incidence of a complication. Cancer was associated with lower adjusted incidence of retinopathy in the colorectal cancer and the combined cohorts, but the reason for this is not immediately clear, and chance finding due to multiple testing cannot be ruled out. As might be expected, cancer was associated with higher all-cause mortality even though we excluded patients who survived less than one year. However, there was no evidence of an adverse impact on diabetes-related mortality. In fact, our findings suggest prostate cancer was associated with lower diabetes mortality in competing risks regression that accounted for death due to other causes.

There are several possible reasons that we found no adverse associations between cancer and diabetes complications or mortality. First, we were able to adjust for differences in baseline characteristics between diabetic cancer patients and diabetic non-cancer controls that otherwise could have confounded associations between cancer and diabetes outcomes. These included baseline BMI, smoking status, HbA1c, cholesterol, and blood pressure. Second, our study was conducted in the UK, which has a robust primary care system in which, under the Quality and Outcomes Framework, (33) there are financial incentives for GPs to provide high quality diabetes care throughout the continuum of care for other conditions such as cancer.

Our study has several strengths, which are attributable largely to the high quality of the database we used. Notably, because the study was based on CPRD, we were able to adjust for additional clinical factors typically not available in US health insurance claims databases, which

otherwise may have confounded associations between cancer and the outcomes of diabetes. These included baseline BMI, smoking status, blood pressure, cholesterol, and HbA1c. In addition, we had rich data about clinical outcomes over a relatively long period of time. Our study also has several limitations. First, at the time it was conducted, we were unable to link the CPRD data to information from the National Cancer Intelligence Network (NCIN), which would have given us details on cancer stage and initial treatment. Although primary care data have a high sensitivity and specificity for identifying cancer (42), registry data would have allowed us to exclude cancer patients diagnosed with metastatic disease. We considered using Read codes in the primary care data files or ICD-10 codes in the Hospital Episode Statistics (HES) inpatient data to stage patients. However, we are not aware of any studies in the UK that validate the use of ICD-10 codes for this purpose, and because only two-thirds of the patients in our study were linked to HES, doing so would have limited our sample sizes for all the analyses. Instead, we excluded patients who died within the first year after their index date. Second, since we did not have access to cancer treatment data we were unable to identify subgroups of cancer patients who may have been at higher risk of diabetes complications or related mortality due to the cancer treatment they received. This should be the subject of further research once linkage to NCIN and chemotherapy databases becomes more readily available. **Third, although we required all patients to have survived at least one year after their index date, requiring longer survival might have enabled us to better assess the longer-term effects of cancer treatment among the cancer patients.** Finally, our findings may not be generalizable to long-term survivors of breast, colorectal, and prostate cancer in an era of full implementation of QOF, which was designed to improve the quality of diabetes primary care, to other countries that do not have primary care performance measures for diabetes care in place, or to other types of cancers.

Conclusions

Overall, incident cancer appears to have had little adverse impact on the long-term outcomes of pre-existing diabetes during 10 years after a diagnosis of breast, colorectal, or prostate cancer. **These findings are important for cancer survivors with pre-existing diabetes because**

they suggest that the advances in cancer therapy and supportive care, which have substantially improved the relative survival of many of the most common types of cancer, are not undermined by excess diabetes morbidity and mortality.

Compliance with Ethical Standards

Funding: This study was funded by the Population Research Committee, Cancer Research UK. Quality and Outcomes of Care for Chronic Conditions in Older Patients Diagnosed with Breast, Colorectal, or Prostate Cancer Compared to Non-Cancer Controls: An Observational Study Using the Clinical Practice Research Datalink (CPRD). Reference # 16609. 1 July 2013–29 February, 2016. In addition, Dr. Keating is supported by K24CA181510 from the US National Cancer Institute.

Conflict of Interest: All authors declare that they have no conflicts of interest.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors. The protocol for this study was approved by the Independent Scientific Advisory Committee (ISAC) to the CPRD on 1 August 2013 (ISAC reference number 13_124) with subsequent amendments approved by ISAC on 22 May 2014. Changes relevant to analyses presented here include identification of diabetes complications through the primary care record, as described above, rather than from hospital data; this change was made because hospital data linkage was not available in all patients. The ISAC protocol was made available to the reviewers and editors during the peer-review process.

Contributions

Guarantor: RIG takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Author Contributions: All authors contributed to the conception and design of the work. RIG and ECM acquired the data. RIG and ECM performed the analyses. All authors contributed to the interpretation of the data for the work. RIG drafted the manuscript. All authors contributed to revising it critically for important intellectual content.

References

1. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33(7):1674-1685.
2. Mills KT, Bellows CF, Hoffman AE, Kelly TN, Gagliardi G. Diabetes and colorectal cancer prognosis: a meta-analysis. *Dis Colon Rectum*, 2013;56(11):1304-1319.
3. De Bruijn KMJ, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CHJ. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *British Journal of Surgery* 2013;100:1421-1429.
4. Peairs KS, Barone BB, Snyder CF, Yeh H-C, Stein KB, Derr RL, Brancati FL, Wolff AC. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol* 2011;29:40-46.
5. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol* 2011;26:863-876.
6. Luo W, Cao Y, Liao C, Gao F. Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies. *Colorectal Disease* 2011;14:1307-1312.
7. Stein KB, Snyder CF, Barone BB, Yeh H-C, Peairs KS, Derr RL, Wolff AC, Brancati FL. Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. *Dig Dis Sci* 2010;55:1839-1851.
8. Snyder CF, Stein KB, Barone BB, Peairs KS, Yeh H-C, Derr RL, Wolff AC, Carducci MA, Brancati FL. Does pre-existing diabetes affect prostate cancer prognosis? A systematic review. *Prostate Cancer and Prostatic Diseases* 2010;13:58-64.
9. Barone BB, Yeh H-C, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. *Diabetes Care* 2010;33(4):931-939.

10. Barone BB, Yeh H-C, Snyder CF, Pearis KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008;300(23):2754-2764.
11. Psarakis HM. Clinical challenges in caring for patients with diabetes and cancer. *Diabetes Spectrum* 2006;19(3):157-162.
12. Keating NL, Liu P-H, O'Malley AJ, Freedland SJ, Smith MR. Androgen deprivation therapy and diabetes control among diabetic men with prostate cancer. *Eur Urol* 2014;65(4):816-824.
13. Hershey DS, Tipton J, Given B, Davis E. Perceived impact of cancer treatment on diabetes self-management. *The Diabetes Educator* 2012;38(6):779-790.
14. Snyder CF, Frick KD, Herbert RJ, Blackford AL, Neville BA, Wolff AC, Carducci MA, Earle CC. Quality of care for comorbid conditions during the transition to survivorship: differences between cancer survivors and noncancer controls. *J Clin Oncol* 2013;31(9):1140-1148.
15. Khan NF, Mant D, Rose PW. Quality of care for chronic diseases in a British cohort of long-term cancer survivors. *Ann Fam Med* 2011;8(5):418-424.
16. Chiao EY, Nambi PV, Naik AD. The impact of diabetes process and outcome quality measures on overall survival in patients with co-morbid colorectal cancer. *J Cancer Surviv* 2010;4(4):381-387.
17. Hanchate AD, Clough-Gorr KM, Ash AS, Thwin SS, Silliman RA. Longitudinal patterns in survival, comorbidity, healthcare utilization and quality of care among older women following breast cancer diagnosis. *J Gen Intern Med* 2010;25(10):1045-1050.
18. Keating NL, Zaslavsky AM, Herrinton LJ, Selby JV, Wolf RE, Ayanian JZ. Quality of diabetes care among cancer survivors with diabetes. *Medical Care* 2007;45(9):869-875.
19. Earle CC, Neville BA. Under use of necessary care among cancer survivors. *Cancer* 2004;101(8):1712-1719.

20. Bayliss EA, Blatchford PJ, Newcomer SR, Steiner JF, Fairclough DL. The effect of incident cancer, depression and pulmonary disease exacerbations on type 2 diabetes control. *J Gen Intern Med* 2011;26(6):575-581.
21. Cancer Research UK. Cancer survival for common cancers.
<http://www.cancerresearchuk.org/health-professional/cancer-statistics/survival/common-cancers-compared#undefined>. Accessed 2/2016.
22. Ning Yi, Shen Qin, Herrick K, Mikkelsen R, Anscher M, Houlihan R, Lapane K. Cause of death in cancer survivors. *Cancer Res* 2012;72(8 Suppl): Abstract nr LB-339.
23. Cancer Research UK. Longer cancer survival means nearly half of cancer patients die from other diseases. <http://www.cancerresearchuk.org/about-us/cancer-news/news-report/2012-04-03-longer-cancer-survival-means-nearly-half-of-cancer-patients-die-from-other-diseases?view=rss>. Accessed 2/2016.
24. Macmillan Cancer Support. Throwing light on the consequences of cancer and its treatment. July 2013. http://www.ncsi.org.uk/wp-content/uploads/MAC14312_CoT_Throwing-light_report_FINAL.pdf. Accessed 2/2016
25. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3): 827–836.
26. Khan NF, Mant D, Carpenter L, Forman D, Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *British Journal of Cancer* 2011;105:S29-S37.
27. Taylor KS, Heneghan CJ, Farmer AJ, Fuller AM, Adler AI, Aronson JK, Stevens RJ. All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large U.K. primary care database. *Diabetes Care* 2013;36(8):2366-2371.
28. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009;339:b4731.

29. Redaniel MTM, Jeffreys M, May MT, Ben-Shlomo Y, Martin RM. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. *Cancer Causes Control* 2012;23:1785-1795.
30. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *British Journal of General Practice* 2011;61(582):e12-e21.
31. Brown AF, Mangione CM, Saliba D, Sarkisian CA: Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 2003;51(Suppl. Guidelines):S265-S280.
32. Kirkman MS, Jones Briscoe V, Clark N, Florez H, Haas LB, Halter JB, Huang ES, Korytkowski MT, Munshi MN, Soule Odegard P, Pratley RE, Swift CS. Diabetes in older adults. *Diabetes Care* 2012;35:2650-2664.
33. Primary Care Commissioning (PCC) QOF Business Rules v25. <http://www.pcc-cic.org.uk/article/qof-business-rules-v25.0> Accessed 2/2016.
34. Adler AI, Stratton IM, Neil HAW, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR on behalf of the UK Prospective Diabetes Study Group. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412-419.
35. Kontopantelis E, Springate DA, Reeves D, Ashcroft DM, Rutter M, Buchan I, Doran T. Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia* 2015;58(3):505-518.
36. Australian Institute of Health and Welfare. <http://www.aihw.gov.au/diabetes-indicators/deaths/>. Accessed January 19, 2016.
37. Ricci-Cabello I, Stevens S, Kontopantelis E, Dalton ARH, Griffiths RI, Campbell JL, Doran T, Valderas JM. Impact of the Prevalence of Concordant and Discordant Conditions on the Quality of Diabetes Care in Family Practices in England. *Ann Fam Med* 2015;13:514-522.

38. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-383.
39. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract* 2010;11(1).
40. Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf* 2009;18(8):704-707.
41. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94(446):496-509.
42. Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiol Drug Saf* 2013;22:168-175.

Figure title and legend

Title. Cumulative incidence of microvascular and macrovascular complications.

Legend. *Microvascular complications consisted of retinopathy, neuropathy, nephropathy, or chronic kidney disease (Stage 4 or 5). Macrovascular complications consisted of peripheral arterial disease, acute myocardial infarction or coronary syndrome, cerebrovascular accident, or lower limb amputation. Cancer patients (red) and controls (blue).

Table 1: Patient Characteristics – Combined Cohorts

Combined Cohorts								
	Cancer (n=3,382)		Control (n=11,135)		All (n=14,517)			
	n	%	n	%	n	%	P-Value	
Age								
50-<60	248	7.3	800	7.2	1,048	7.2	0.740	
60-<70	946	28.0	3,098	27.8	4,044	27.9		
70-<80	1,498	44.3	5,041	45.3	6,539	45.0		
≥80	690	20.4	2,196	19.7	2,886	19.9		
Sex								
Male	1,974	58.4	6,551	58.8	8,525	58.7	0.630	
Female	1,408	41.6	4,584	41.2	5,992	41.3		
Year of Diagnosis								
2000-2004		546	16.1	1,649	14.8	2,195	15.1	0.087
2005-2009		1,500	44.4	4,902	44.0	6,402	44.1	
≥2010	1,336	39.5	4,584	41.2	5,920	40.8		
Smoking Status								
Non Smoker		991	29.3	3,364	30.2	4,355	30	<0.001
Ex Smoker		1,716	50.7	5,633	50.6	7,349	50.6	
Current Smoker			324	9.6	1,240	11.1	1,564	10.8

Not Reported	351	10.4	898	8.1	1,249	8.6
--------------	-----	------	-----	-----	-------	-----

Body Mass Index

<25	579	17.1	1,932	17.4	2,511	17.3	<0.001
-----	-----	------	-------	------	-------	------	--------

25-<30	1,272	37.6	4,183	37.6	5,455	37.6
--------	-------	------	-------	------	-------	------

≥30	1,344	39.7	4,656	41.8	6,000	41.3
-----	-------	------	-------	------	-------	------

Not Reported	187	5.5	364	3.3	551	3.8
--------------	-----	-----	-----	-----	-----	-----

Charlson Comorbidity Index

1-2	1,878	55.5	5,898	53.0	7,776	53.6	0.024
-----	-------	------	-------	------	-------	------	-------

3-4	1,044	30.9	3,578	32.1	4,622	31.8
-----	-------	------	-------	------	-------	------

>4	460	13.6	1,659	14.9	2,119	14.6
----	-----	------	-------	------	-------	------

Type of Cancer (or Control)

Breast	1,036	30.6	3,194	28.7	4,230	29.1	<0.001
--------	-------	------	-------	------	-------	------	--------

Colorectal	1,069	31.6	4,047	36.3	5,116	35.2
------------	-------	------	-------	------	-------	------

Prostate	1,277	37.8	3,894	35.0	5,171	35.6
----------	-------	------	-------	------	-------	------

Type of Diabetes

Type I	141	4.2	554	5.0	695	4.8	0.054
--------	-----	-----	-----	-----	-----	-----	-------

Type II	3,241	95.8	10,581	95.0	13,822	95.2
---------	-------	------	--------	------	--------	------

Any Microvascular Complication

No 2,412 71.3 7,750 69.6 10,162 70.0 0.056

Yes 970 28.7 3,385 30.4 4,355 30.0

Any Macrovascular Complication

No 2,681 79.3 8,684 78.0 11,365 78.3 0.113

Yes 701 20.7 2,451 22.0 3,152 21.7

Any Antidiabetic Agent

No 769 22.7 2,363 21.2 3,132 21.6 0.060

Yes 2,613 77.3 8,772 78.8 11,385 78.4

Blood Pressure \leq 140/80 mm Hg

Yes 2,026 59.9 6,770 60.8 8,796 60.6 <0.001

No 1,250 37.0 4,252 38.2 5,502 37.9

Not Reported 106 3.1 113 1.0 219 1.5

Systolic mean(SD) 3,276 136(15) 11,022 136(16) 14,298
136(16) 0.205

Diastolic mean(SD) 3,276 74(9) 11,022 74(9) 14,298 74(9) 0.090

Total Cholesterol \leq 5mmol/L

Yes 2,706 80.0 8,971 80.6 11,677 80.4 <0.001

No 475 14.0 1,826 16.4 2,301 15.9

Not Reported	201	5.9	338	3.0	539	3.7
--------------	-----	-----	-----	-----	-----	-----

mean(SD)	3,181	4.2(0.94)	10,797	4.3(1.57)	13,978	4.2(1.45)
	<0.001					

HbA1c(mmol/mol)

≤59	2,179	64.4	6,995	62.8	9,174	63.2	0.362
-----	-------	------	-------	------	-------	------	-------

59-≤64	310	9.2	1,054	9.5	1,364	9.4
--------	-----	-----	-------	-----	-------	-----

65-≤75	322	9.5	1,074	9.6	1,396	9.6
--------	-----	-----	-------	-----	-------	-----

>75	185	5.5	702	6.3	887	6.1
-----	-----	-----	-----	-----	-----	-----

Not Reported	386	11.4	1,310	11.8	1,696	11.7
--------------	-----	------	-------	------	-------	------

mean(SD)	2,996	54.0(12.5)	9,825	54.5(13.1)	12,821	54.3(13.0)	0.060
----------	-------	------------	-------	------------	--------	------------	-------

SD Standard Deviation; HbA1c Glycosylated hemoglobin

Table 2: Multivariate Analyses of Complications

Type of Complication	Cohort			Adjusted Hazard Ratio [95% CI]
	Combined	Breast	Colorectal	
	Unadjusted Hazard Ratio [95% CI]	Unadjusted Hazard Ratio [95% CI]	Unadjusted Hazard Ratio [95% CI]	Unadjusted Hazard Ratio [95% CI]
	Adjusted Hazard Ratio [95% CI]	Adjusted Hazard Ratio [95% CI]	Adjusted Hazard Ratio [95% CI]	Adjusted Hazard Ratio [95% CI]

Any Microvascular	0.96	0.99	1.03	1.04	1.01	1.02	0.89	0.94	
	[0.87-1.06]	[0.89-1.09]	[0.86-1.23]		[0.86-1.25]		[0.85-1.20]	[0.85-1.22]	
	[0.76-1.05]	[0.80-1.11]							
Chronic Kidney Disease		1.08	1.13	1.23	1.22	0.94	1.05	1.01	1.11
	[0.85-1.36]	[0.89-1.43]	[0.83-1.82]		[0.81-1.82]		[0.62-1.44]	[0.68-1.64]	
	[0.68-1.51]	[0.74-1.68]							
Nephropathy	1.12	1.19	1.16	1.19	1.71	1.82	0.65		
	[0.66-1.88]	[0.70-2.02]		[0.41-3.28]		[0.41-3.45]		[0.78-3.73]	[0.83-3.98]
	[0.25-1.70]								
Neuropathy	1.07	1.10	1.22	1.23	1.31	1.30	0.83	0.84	
	[0.88-1.31]	[0.90-1.35]		[0.85-1.76]		[0.85-1.78]		[0.96-1.81]	[0.94-1.80]
	[0.59-1.17]	[0.59-1.18]							
Retinopathy	0.86**	0.88*	0.96	0.97	0.82	0.81*	0.83*	0.89	
	[0.77-0.96]	[0.79-0.98]		[0.79-1.17]		[0.79-1.18]		[0.67-1.00]	[0.66-0.99]
	[0.69-0.99]	[0.74-1.06]							
Any Macrovascular	0.94	0.96	1.04	1.00	0.92	0.94	0.93	0.98	
	[0.80-1.11]	[0.82-1.13]	[0.77-1.40]		[0.74-1.37]		[0.69-1.21]	[0.71-1.24]	
	[0.72-1.21]	[0.75-1.26]							
Acute Myocardial Infarction		1.09	1.11	0.82	0.79	1.42	1.37	1.03	1.12
	[0.87-1.37]	[0.88-1.39]	[0.50-1.32]		[0.48-1.29]		[0.99-2.04]	[0.94-1.99]	
	[0.72-1.49]	[0.77-1.62]							

Cerebrovascular Accident	0.99	0.99	1.33	1.42	0.90	0.97	0.87	
	[0.78-1.25]	[0.78-1.26]	[0.87-2.03]	[0.92-2.17]	[0.59-1.37]	[0.64-1.47]		
	[0.59-1.28]							
Lower Limb Amputation	0.76	0.83	0.51	0.45	1.18	1.21	0.55	0.62
	[0.45-1.29]	[0.49-1.42]	[0.11-2.28]	[0.10-2.09]	[0.56-2.49]	[0.53-2.74]		
	[0.23-1.31]	[0.25-1.52]						
Peripheral Arterial Disease	0.74*	0.78	0.99	0.94	0.60*	0.66	0.79	0.86
	[0.56-0.97]	[0.59-1.03]	[0.56-1.74]	[0.52-1.72]	[0.36-1.00]	[0.39-1.10]		
	[0.52-1.18]	[0.57-1.30]						

CI Confidence Interval

*P <0.05- **P <0.01- ***P <0.001

Table 3: Multivariate Survival Analyses

Cohort			
Combined	Breast	Colorectal	Prostate
Unadjusted Hazard Ratio [95% CI]	Adjusted Hazard Ratio [95% CI]		Unadjusted Hazard Ratio [95% CI]
Hazard Ratio [95% CI]	Adjusted Hazard Ratio [95% CI]		Unadjusted Hazard Ratio [95% CI]
Adjusted Hazard Ratio [95% CI]	Unadjusted Hazard Ratio [95% CI]		Adjusted Hazard Ratio [95% CI]
Hazard Ratio [95% CI]			

Mortality

All Cause	1.47***	1.57***	1.47**	1.52***	1.64***	1.71***
	1.44***	1.60***				
	[1.33-1.63]	[1.41-1.74]	[1.21-1.80]	[1.24-1.85]	[1.38-1.95]	[1.43-2.04]
	[1.22-1.72]	[1.35-1.91]				
Diabetes	0.73**	0.76***	0.87	0.91	0.88	0.87
			0.57**	0.61***		
	[0.59-0.90]	[0.61-0.94]	[0.58-1.31]	[0.59-1.40]	[0.63-1.23]	[0.62-1.23]
	[0.40-0.82]	[0.43-0.88]				

* p < 0.05- ** p < 0.01- *** p < 0.001